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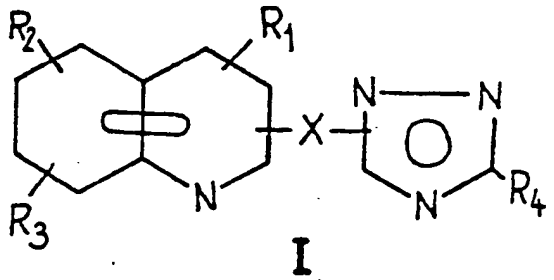

I (I)

(57) Abstract

New triazolyl quinoline derivatives and acid addition salts thereof (wherein R^1 stands for hydrogen, methyl, trihalogenomethyl or carboxy; R^2 is hydrogen, halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, phenoxy, amino, acetamino, C_{1-4} dialkylamino, acetyl, benzoyl, methylthio, carboxy, cyano, ethoxycarbonyl, nitro or trihalogenomethyl; R^3 represents hydrogen, C_{1-4} alkyl or C_{1-4} alkoxy; R^4 stands for hydrogen, methyl or ethyl and X stands for a valency bond or -S-). The new compounds of general formula (I) possess valuable analgesic, antiphlogistic and fungicidal effect and can be used both in therapy and agriculture.

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TRIAZOLYL QUINOLINE DERIVATIVES

This invention relates to new triazolyl quinoline derivatives, a process for the preparation thereof and pharmaceutical and fungicidal compositions containing the same.

According to an aspect of the present invention there are provided new triazolyl quinoline derivatives and acid addition salts thereof (wherein

R^1 stands for hydrogen, methyl, trihalogenomethyl or carboxy;

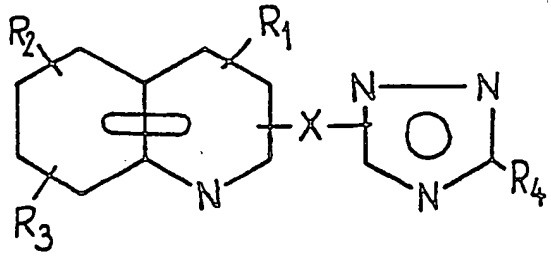
R^2 is hydrogen, halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, phenoxy, amino, acetamino, C_{1-4} dialkylamino, acetyl, benzoyl, methylthio, carboxy, cyano, ethoxycarbonyl, nitro or trihalogenomethyl;

R^3 represents hydrogen, C_{1-4} alkyl or C_{1-4} alkoxy;

R^4 stands for hydrogen, methyl or ethyl and

X stands for a valency bond or -S-)

According to a further aspect of the present invention there is provided a process for the preparation of compounds of the general Formula (I)



(I)

(wherein R^1, R^2, R^3, R^4 and X are as stated above)

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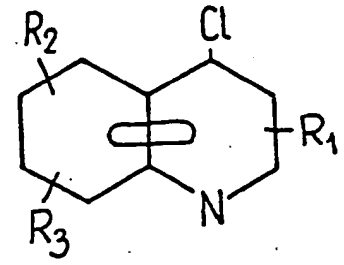
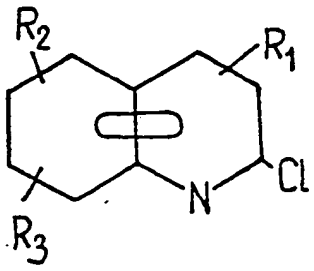
and acid addition salts thereof which comprises reacting a halogeno quinoline derivative of the general formula (II)



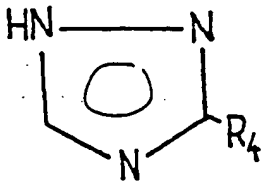
(II)

or (III)



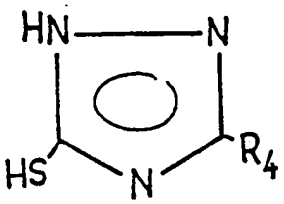
(III)

(wherein R^1, R^2 and R^3 are as stated above) with a 1,2,4-triazole of the general Formula (IV)



(IV)

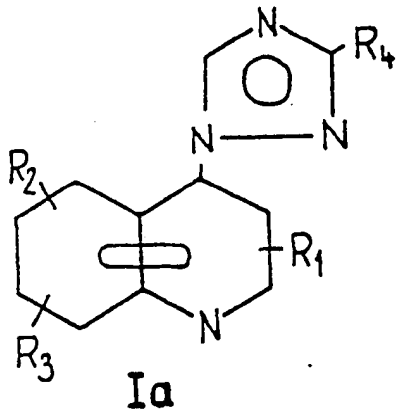
or (V)



(V)

(wherein R^4 is as stated above) in the presence or absence of a solvent, in the presence or absence of an acid or a base, at a temperature between 0 °C and 200 °C and if desired isolating the product thus obtained in the form of the free base or an acid addition salt thereof.

According to a feature of the process of the present invention there is provided a process for the preparation of compounds of the general Formula (Ia)

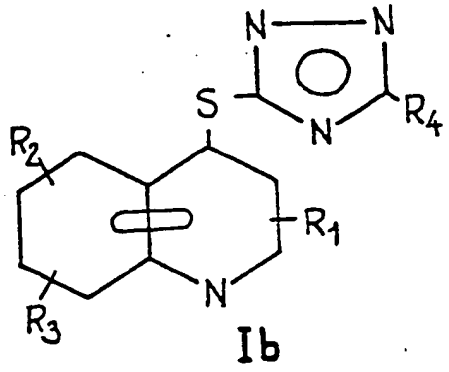


(Ia)

Ia

which comprises reacting a 4-chloro-quinoline derivative of the general formula (II) with a 1,2,4-triazole of the general Formula (IV) (wherein R^1, R^2, R^3 and R^4 are as stated above).

According to a further feature of the process of the present invention there is provided a process for the preparation of compounds of the general Formula (Ib)

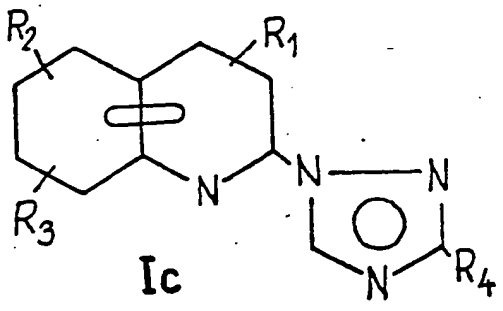


(Ib)

Ib

which comprises reacting a 4-chloro-quinoline derivative of the general Formula (II) with a 3--mercapto-1,2,4-triazole of the general Formula (V) (wherein R^1, R^2, R^3 and R^4 are as stated above).

According to a still further feature of the process of the present invention there is provided a process for the preparation of compounds of the general Formula (Ic)



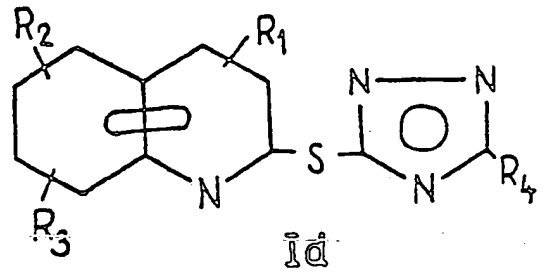
(Ic)

Ic

which comprises reacting a 2-chloro-quinoline of the general Formula (III) with a 1,2,4-triazole of the general Formula (IV) (wherein R^1, R^2, R^3 and R^4 are as stated above).

According to a still further feature of the process of the present invention there is

provided a process for the preparation of compounds of the general Formula (Id)



(Id)

Id

which comprises reacting a 2-chloro-quinoline derivative of the general Formula (III) with a 3-mercapto-1,2,4-triazole of the general Formula (V) (wherein R^1, R^2, R^3 and R^4 are as stated above).

The starting materials used in the process of the present invention are known compounds. The prior art references of the starting materials are as follows:

4-chloro-quinolines of the general Formula (II): "The Chemistry of Heterocyclic Compounds" Vol. 32 Quinolines Part I pages 391 - 398; the references cited therein; Hungarian patent applications Ser. No. 3869/82 and 4003/82.

2-chloro-quinolines of the general Formula (III): "The Chemistry of Heterocyclic Compounds" Vol. 32 Quinolines Part I pages 387-390: J. Chem. Soc. P.I. 1981 1(5) 1537-1543.

1H-1,2,4-triazoles of the general Formula (IV): Hungarian patent application Ser. No. 4370/83; DOS No. 2,802,491; Chem. Ber. 1968, 101 (6) 2033-2036.

3(5)-mercapto-1,2,4-triazoles of the general Formula (V): Liebigs. Ann. Chem. 637, 133 135-165 (1960).

The new compounds of the general Formula (I) possess valuable biological properties and exhibit useful analgesic and antiphlogistic effect. Some representatives of the compounds of the general Formula (I) are highly active against phytopathogenic fungal pests according to both in vivo and in vitro tests.

It has been found that the reaction between 4- and 2-chloro-quinoline derivatives of the general Formula (II) or (III), respectively, comprising only electron repulsing substituents (e.g. methyl or methoxy groups) and 1H-1,2,4--triazoles or 3(5)-mercapto-1H-1,2,4-triazoles of the general Formula (IV) or (V), respectively, is autocatalytic whereby the hydrochloric acid formed in the course of the reaction acts as catalyst. The reaction can also be catalysed by other acids, particularly strong mineral or organic acids or acidic salts (e.g. sulfuric acid, trifluoroacetic acid or ammonium chloride). It is preferred to carry out the reaction in the presence of the said acidic compounds - particularly hydrochloric acid - which can be used in the range of from catalytic to stochiometrical amount.

If less basic chloro quinolines comprising electron attracting group or groups (e.g. chlorine, trifluoromethyl) are used, such catalysis is not observed. In this case, however, the reaction may be facilitated by carrying out the same in the presence of an organic or inorganic base (e.g. triethyl amine, potassium carbonate or sodium hydroxide) used in stochiometrical or higher amount. This pertains also to the case if the 1H-1,2,4-triazole or 3(5)-mercapto-1H-1,2,4-triazole

derivative is used in the form of an alkali salt (e.g. sodium salt) thereof.

It has been found furtheron that the mercapto group is more reactive than the -NH- -group of the triazole ring.

The reaction (preparation of compounds of the general Formulae (Ia), (Ib), (Ic) and (Id)) may be carried out preferably in the presence of a polar organic solvent (e.g. ethanol, acetone, acetonitrile, dimethyl formamide, dimethyl sulfoxide etc). As reaction medium an apolar organic solvent (e.g. benzene, toluene, chloro benzene, dichloro benzene) may also be used and one may also work in the absence of an organic solvent in the melt.

The reaction of the present invention may be carried out at a temperature between 0 °C and 200 °C, preferably in the range of 20 - 150 °C. The reaction temperature is selected under taking into consideration the properties of the reactants and the method used.

It is sufficient to react the chloro quinoline component with a molar equivalent amount of the 1H-1,2,4-triazole or 3(5)-mercapto-1,2,4- -triazole but the reactions generally take place more rapidly and completely if the starting material of the general Formula (IV) or (V) is used in a 1-2 molar equivalent amount.

According to a form the realization of the process of the present invention the reaction components are melt and the reaction having been terminated the product formed is isolated. According to the said embodiment of the process the product is formed in the form of the hydrochloride thereof. The direct reaction product is treated

with an apolar organic solvent (e.g. ether, chloroform, benzene, hexane) or crystallized from a polar solvent (e.g. ethanol, methanol, acetonitrile, dimethyl formamide) or a mixture of polar and apolar solvents.

The free base of the general Formula (I) may be isolated by cooling the reaction mixture, dissolving in water or a mixture of water and ethanol - preferably under adding a mineral or organic acid - and precipitating the product by adding an organic or inorganic base. The crude product may be crystallized from a mixture of a polar organic solvent and water or polar and apolar organic solvents.

According to a further embodiment of the process of the present invention the reaction partners are reacted in the presence of an apolar organic solvent (e.g. benzene, toluene, xylene, hexane, carbon tetrachloride, chloro benzene, dichloro benzene etc). The reaction having been completed the product precipitated in the form of the hydrochloride is filtered, if necessary crystallized and converted into the free base as described above.

According to a still further embodiment of the process of the present invention the reaction partners are reacted in a polar organic solvent (e.g. ethanol, ethylene glycol, acetonitrile, acetone, ethyl methyl ketone, dimethyl formamide, dimethyl sulfoxide, glacial acetic acid). The product is isolated in the form of the free base or a salt formed with a mineral acid.

According to a preferred embodiment of the process of the present invention the reaction is accomplished in a polar organic solvent (e.g.

ethanol, ethylene glycol, acetonitrile, acetone, methyl ethyl ketone, dimethyl formamide), preferably in the presence of hydrochloric acid.

The acidic medium may be either provided by introducing an acid (preferably hydrochloric acid) to the reaction mixture or by using the chloro quinoline component in the form of a salt (preferably hydrochloride) thereof. The product formed in the form of a salt may be isolated from the reaction mixture according to one of the methods set forth above.

According to a further preferable form of realization of the present process of the invention the reaction is accomplished in a polar organic solvent, in the presence of a molar equivalent or larger amount of a strong base (e.g. triethyl amine, potassium carbonate, sodium carbonate etc).

The above reaction may also be carried out by using the triazole or mercapto triazole of the general Formula (IV) or (V), respectively, in the form of an alkali (e.g. sodium or potassium) salt thereof.

The structure of the new compounds prepared by the process of the present invention is characterized and confirmed by means of NMR, IR and MS spectrum and the purity of the product is determined by thin layer, gas and liquid chromatography.

The compounds of the general Formula (I) possess valuable physiological properties and eliminate or efficiently relieve induced pain and inflammation processes. The significant advantage of the compounds of the general Formula (I) is that in analgesic and antiphlogistic dose range

ulcerative activity is observed not at all or but to a very small extent.

Thus the orally administered compounds of the general Formula (I) efficiently reduce acute inflammatory processes. According to the method of Winter [Proc. Soc. Exp. Biol. Med. 111, 544 (1962)] carrageenin oedema is induced and evaluated on male Wistar rats fasted for 16 hours (body weight 160 - 180 g). Percental inhibition is calculated from the average oedema values of the groups treated with the test compound on the one hand and with carrier (carboxy methyl cellulose, CMC; control) on the other. ED_{50} values are determined by means of regression analysis of the inhibition values. The test compounds are administered through a stomach canule in the form of a 1 % carboxy methyl cellulose (CMC) suspension, one hour before introducing the carrageenin injection. The carrageenin oedema inhibiting effect of the test compounds are summarized in Table I.

The protecting effect of the test compounds against adjuvant induced arthritis is shown in Table II. According to the method of Newbold 0.1 ml of Freund complet adjuvant (Difco Lab. Mich. USA) is injected to the plantar surface of the right hind paw of male Wistar rats weighing 160 - - 200 g. The volume of the hind paws is measured before and 21 days after the administration of the adjuvant with the aid of a mercury plethysmometer. The test compound is administered to the test animals for two weeks in a daily oral dose of 25 mg/kg. In Table II the "percental inhibition of the growth of paw volume" relates to the value determined on the 21st day.

In the adjuvant arthritis test, considered

to be the best model test of rheumatoidal arthritis, the compounds of the present invention inhibit articular deformations more effectively than the reference substances Naproxen and Phenylbutazon. The tests show furthermore that the compounds of the present invention are active not only in healing morphological deformations but effect in a desirable and useful manner the functional condition and fitness of the feet, moreover the general physical state and condition of the animals, too.

The analgesic effect of the compounds of the present invention is tested according to the hot (56 °C) plate test on male and female CFLP strain mice weighing 18 - 22 g. The point of time of the appearence of the deterring reaction (Abwehrreaktion) is determined and related to the latent time measured on the control group (Woolfe and McDonald 1944). At least 10 animals are used per dose. The test compounds are administered orally 60 minutes before the test in the form of a 1 % methyl cellulose suspension. The results are summarized in Table III. The test is carried out on separated male Wistar rats weighing 180 - 210 g and fasted for 16 hours. The test compounds are suspended in 1 % carboxy methyl cellulose and administered orally in a dose of 10 ml/kg.

Five hours after treatment the animals are sacrificed and their stomachs are placed into a 2.5 % formaline solution. The number and rate of punctiform haemorrhage and ulcers is evaluated according to the following scale:

0 = no lesion;
1 = some punctiform haemorrhage ($\leq$ 10);
2 = diffuse haemorrhage or small ulcer ($\leq$ 2 mm);
3 = two or more minor small ulcer ($\leq$ 2 mm);

4 = one or more large ulcer (> 2 mm).

In a dose of 25 mg/kg and 100 mg/kg the compounds of the present invention do not exhibit ulcerogenic effect. In acute test the UD_{50} value of Naproxen and Indomethacin amounts to 20.8 mg/kg and 6.3 mg/kg p.o., respectively.

The acute toxicity of the compounds of the general Formula (I) is determined according to the method of Litchfield - Wilcoxon on male and female rats of CFLP strain. The LD_{50} values vary between 500 and 2000 mg/kg p.o.

According to a further aspect of the present invention there are provided pharmaceutical compositions comprising in an effective amount at least one compound of the general Formula (I) (wherein R^1, R^2, R^3, R^4 and X are as stated above) or a pharmaceutically acceptable acid addition salt thereof as active ingredient in admixture with suitable inert solid or liquid pharmaceutical carriers.

The pharmaceutical compositions may be prepared in a manner known per se by admixing at least one compound of the general Formula (I) or a pharmaceutically acceptable acid addition salt thereof with suitable inert solid or liquid pharmaceutical carriers.

The compounds of the present invention may be used in therapy preferably for the treatment of various rheumatic diseases, particularly rheumatoidal arthritis, spondylitis, osteortrosis and gout. The active ingredient may be finished by known methods of pharmaceutical industry in forms suitable for enteral or parenteral administration (.e.g. tablets, capsules, dragées, injec-

tions etc.). The pharmaceutical compositions of the present invention may optionally comprise one or more further biologically active materials in addition to the compound of the general Formula (I). The compositions comprise carriers and excipients generally used in therapy.

The dose of the compounds of the general Formula (I) varies between wide ranges and depends on several factors (e.g. body weight, age and condition of the patient etc). The dose amounts generally to 10 - 200 mg/kg body weight (enteral administration) and to 1 - 50 mg/kg (parenteral administration). The above ranges are, however, just of an informative character.

The compounds of the general Formula (I) possess considerable antifungal activity, too, and are active against phytopathogenic fungal strains and diseases. The compounds of the general Formula (I) are particularly effective against powdery mildew. In Table IV the activity of some compounds of the general Formula (IV) against Erysiphe graminis f. sp. tritici strain are disclosed.

The following test method is used:
Glasshouse conditions: temperature 20 °C; relative humidity 80 %; strength of illumination 6000 lux. The test plants (MV-9 Automn wheat) are cultivated in pots (diameter 20 cm) in a 1:1 mixture of sand and perlite. The average number of plants per pot amounts to 180, the height of the plants is 6-7 cm. About 8 ml of the aqueous suspension of the test compound is applied onto the plants with the aid of a sprayer.

The rate of infectedness is determined after 8 days. Activity is calculated from the percental inhibition values. As control commercial

products Fundazol 50 WP and Karathene LC 50 are used.

According to a further feature of the present invention there are provided fungicidal compositions comprising as active ingredient in an effective amount at least one compound of the general Formula (I) (wherein R^1, R^2, R^3, R^4 and X are as stated above) or an acid addition salt thereof in admixture with suitable inert solid or liquid carriers or diluents.

The said fungicidal compositions are prepared by methods known per se.

Table I

Antiphlogistic effect on carrageenin induced oedema on rats

Test compound No.	Dose mg/kg p.o.	Percental inhibition of paw volume	ED_{50} mg/kg p.o.
61	12.5	29	60.9
	25.0	37	
	100.0	58	
62	12.5	18	38.4
	25.0	51	
	50.0	59	
	100.0	69	
64	12.5	15	59.1
	25.0	27	
	50.0	44	
	100.0	65	

Table I
(contd.)

Test compound No.	Dose mg/kg p.o.	n	Percental inhibition of paw volume	ED_{50} mg/kg p.o.
69	12.5		27	35.0
	25		33	
	50		52	
	100		86	
74	12.5		26	25.7
	25		55	
	50		69	
83	12.5		21	28.1
	25		63	
	50		70	
	100		72	
107	12.5		29	30.6
	25		40	
	50		70	
	100		74	
108	12.5	10	19	38.5
	25	10	45	
	50	10	61	
	100	10	70	
110	12.5	10	10	51.4
	25	10	42	
	50	10	46	
	100	10	61	

Table I
(contd.)

Test compound No.	Dose mg/kg p.o.	n	Percental inhibition of paw volume	ED_{50} mg/kg p.o.
Phenylbutazon	25	10	21	100.9
	50	15	42	
	100	15	45	
	200	15	66	
Naproxen	12.5	15	33	28.7
	25	15	49	
	50	15	64	
	100	15	71	
Indomethacin	1	10	28	4.1
	2	10	40	
	4	10	47	
	8	10	64	
	12	10	67	

n = number of the test animals

Table II
Inhibitory effect on adjuvant induced arthritis on rats

Test compound No.	Dose mg/kg p.o.	n	Percental inhibition of the growth of paw volume, on the 21st day
46	25	10	28.1
61	25	10	38.2
62	25	10	40.3

Table II
(contd.)

Test compound No.	Dose mg/kg p.o.	n	Percental inhibition of the growth of paw volume, on the 21st day
64	25	10	40.6
67	25	10	32.8
69	25	10	35.2
83	25	12	46.7
85	25	12	28.4
107	25	12	17.8
108	25	12	35.2
109	25	12	36.7
110	25	12	32.1
138	25	10	35.2
Phenylbutazon	50	15	18.5
Naproxen	12.5	15	16.8
	25	15	28.4

n = number of the test animals

Table III
Hot plate test, on mice

Test compound No.	Dose mg/kg p.o.	Lengthening of reaction time in %
	25	7
46	50	18
	100	38

Table III
(contd.)

Test compound No.	Dose mg/kg p.o.	Lengthening of reaction time in %
61	25	20
	50	22
	100	26
62	12.5	17
	25	19
	50	30
	100	38
64	25	17
	50	39
	100	44
69	25	13
	50	24
	100	30
74	25	19
	50	26
	100	43
83	25	16
	50	28
	100	59
107	25	34
	50	41
	100	88
108	25	34
	50	46
	100	46

Table III
(contd.)

Test compound No.	Dose mg/kg p.o.	Lengthening of reaction time in %
110	25	21
	50	34
	100	52
138	25	25
	50	37
	100	82
Phenylbutazon	100	29
	150	42
	200	44
Naproxen	12.5	25
	25	31
	50	45
	100	49

Table IV

In vitro antifungal effect on Erysiphe graminis test organism

Test compound No.	Concentration /ug/ml	Inhibition %	ED_{50} /ug/ml
1	37.5	50.6	32.9
	50	72.6	
	75	83.0	
	100	85.3	
	150	86.8	
	200	90.1	
	400	99.6	
8	25	42.1	31.1
	50	70.9	
	100	82.0	
	150	84.1	
	200	91.9	
	400	98.8	
10	25	20.3	56.9
	50	42.8	
	100	76.4	
	200	92.7	
	400	90.1	
6	25	49.2	27.9
	50	71.6	
	100	85.1	
	200	89.5	
	400	99.4	

Table IV
(contd.)

Test compound No.	Concentration /ug/ml	Inhibition %	ED_{50} /ug/ml
22	25	40.8	31.2
	50	67.7	
	100	79.8	
	200	93.0	
	400	96.9	
Karathane LC 50	12.5	24.9	27.4
	25	46.2	
	50	72.7	
	100	87.9	
Chinoin fundazol 50 WP	50	55.3	41.2
	100	72.6	
	200	89.1	
	400	94.6	

Further details of the present invention are to be found in the following Examples without limiting the scope of protection to the said Examples.

Example 1

4-(1H-1,2,4-triazole-1-yl)-7-chloro--quinoline

A mixture of 1.98 g of 4,7-dichloro--quinoline, 1,38 g of 1,2,4-triazole and 10 ml of dimethyl formamide is stirred at 100 °C for 6 hours, whereupon the reaction mixture is poured into 100 ml of water and neutralized with 1 ml of a concentrated ammonium hydroxide solution. The precipitated product is filtered and recrystallized from ethanol. Thus 1.61 g of the desired product are obtained, yield 70 %, Mp.: 169 - 170 °C.

Example 2

4-(1H-1,2,4-triazole-1-yl)-2,8-dimethyl--quinoline

A mixture of 1.91 g of 2,8-dimethyl-4--chloro-quinoline and 1.38 g of 1,2,4-triazole is melt at 120 °C and stirred for 2 hours. The solidified melt is dissolved in a mixture of ethanol and water. The solution is poured into a solution of 0.84 g of sodium bicarbonate and 20 ml of water. The precipitated product is filtered. Thus 1.97 g of the desired compound are obtained, yield 88 %, m.p.: 99 - 100 °C.

Example 3

4-(1H-1,2,4-triazole-1-yl)-2-methyl-6--methoxy-quinoline

A mixture of 2.44 g of 2-methyl-4-chloro-

-6-methoxy-quinoline-hydrochloride, 1.38 g of 1,2,4-triazole and 10 ml of dimethyl formamide is stirred at 80 °C for 3 hours whereupon the reaction mixture is poured into 100 ml of water and neutralized with 2 ml of a concentrated ammonium hydroxide solution. The precipitated product is filtered. Thus 2.09 g of the desired compound are obtained, yield 87 %, mp.: 117 - 118 °C.

Example 4

4-(1H-1,2,4-triazole-1-yl)-2-methyl-6,8--dichloro-quinoline

A mixture of 2.46 g of 2-methyl-4,6,8--trichloro-quinoline, 1.82 g of the sodium salt of 1,2,4-triazole and 10 ml of dimethyl formamide is stirred at 100 °C for 25 hours whereupon the reaction mixture is poured into 100 ml of water. The precipitated product is filtered. Thus 2.59 g of the desired compound are obtained, yield 93 %. Mp.: 220 - 222 °C.

Example 5

4-(1H-1,2,4-triazole-1-yl)-2,8-bis-trifluoromethyl-quinoline

A mixture of 3.0 g of 4-chloro-2,8--bis-trifluoromethyl-quinoline, 1.38 g of 1,2,4--triazole, 1.38 g of potassium carbonate and 30 ml of acetone is heated to boiling for 23 hours whereupon the reaction mixture is poured into 100 ml of water. The precipitated product is filtered, dissolved in 5 ml of ethanol, whereupon 5 ml of water are added. The precipitated product is filtered. Thus 2.42 g of the desired compound are obtained, yield: 73 %, mp.: 106 - 107 °C.

Example 6

4-[1H-1,2,4-triazole-3(5)-yl-5(3)--mercapto]-2-trichloromethyl-8-chloro-quinoline

A mixture of 3.16 g of 2-trichloromethyl--4,8-dichloro-quinoline, 1.48 g of the sodium salt of 3(5)-mercapto-1,2,4-triazole and 10 ml dimethylformamide is stirred at 100 °C for 18 hours. The reaction having been completed the reaction mixture is poured into water, the precipitated product is filtered and recrystallized from ethanol. Thus 2.1 g of the desired compound are obtained, yield 55 %, M.p.: 188 - 183 °C.

Example 7

4-[5(3)-ethyl-1H-1,2,4-triazole-3(5)-yl--mercapto]-2,8-dimethyl-quinoline

A mixture of 1.32 g of 4-chloro-2,8-dimethyl-quinoline, 1.55 g of 3(5)-mercapto-5(3)--ethyl-1,2,4-triazole and 20 ml of ethanol is stirred at 30 °C for 20 hours. The reaction mixture is poured into 50 ml of water, neutralized with 1 ml of concentrated ammonium hydroxide and the precipitated product is filtered. Thus 2.41 g of the desired compound are obtained, yield 85 %, mp.: 176 - 177 °C.

Example 8

2-(1H-1,2,4-triazole-1-yl)-3-methyl--quinoline

A mixture of 1.78 g of 2-chloro-3-methyl--quinoline and 0.69 g of 1,2,4-triazole is melt and allowed to stand at 120 °C for 4 hours. The melt is cooled, then dissolved in 10 ml of ethanol, poured into 20 ml of water and neutralized with 1 ml of

concentrated ammonium hydroxide. The precipitated product is filtered. Thus 1.49 g of the desired compound are obtained, yield 71 %. Mp.: 80 - 81 °C.

Example 9

2-(1H-1,2,4-triazole-1-yl)-4-methyl--quinoline hydrochloride

A mixture of 1.78 g of 2-chloro-4-methyl--quinoline, 0.76 g of 1,2,4-triazole and 10 ml of chloro benzene is stirred at 100 °C for 7 hours. The reaction mixture is cooled, the precipitated product is filtered, dissolved in 5 ml of ethanol and precipitated by adding 10 ml of ethyl ether. The precipitated product is filtered. Thus 1.72 g of the desired compound are obtained, yield 70 %. Mp.: 193 - 194 °C.

Example 10

2-(1H-1,2,4-triazole-1-yl)-7-chloro-3,8--dimethyl-quinoline

A mixture of 2.26 g of 2,7-dichloro-3,8--dimethyl-quinoline, 1,1 g of the sodium salt of 1,2,4-triazole and 10 ml of dimethyl formamide is stirred at 100 °C for 25 hours. The reaction mixture is poured into 100 ml of water and the precipitated product is filtered. Thus 2.48 g of the desired compound are obtained, yield 96 %. Mp.: 147 - - 148 °C.

Example 11-

2-(3-methyl-1H-1,2,4-triazole-1-yl)-4,6--bis-trichloromethyl-quinoline

A mixture of 3.99 g of 2-chloro-4,6-bis--trichloromethyl-quinoline, 1.26 g of the sodium salt of 3-methyl-1,2,4-triazole and 10 ml of dimethyl

formamide is stirred at 100 °C for 20 hours. The reaction mixture is poured into 100 ml of water, the precipitated product is filtered and recrystallized from 10 ml of ethanol. Thus 2.76 g of the desired compound are obtained, yield 62 %. M.p.: 169 - 170 °C.

Example 12

2-[5(3)-methyl-1H-1,2,4-triazole-3(5)--yl-mercapto]-3-methyl-quinoline-hydrochloride

A mixture of 1.78 g of 2-chloro-3-methyl--quinoline, 1.38 g of 3(5)-mercapto-5(3)-methyl--1,2,4-triazole and 10 ml of chloro benzene is stirred at 100 °C for 2 hours. The reaction mixtur is cooled, the precipitated product is filtered and washed with diethyl ether. Thus 2.8 g of the desired compound are obtained, yield 96 %, mp.: 190 - 192 °C.

Example 13

2-[1H-1,2,4-triazole-3(5)-yl-mercapto]--4,8-dimethyl-quinoline-hydrochloride

A mixture of 1.92 g of 2-chloro-4,8--dimethyl-quinoline and 1.21 g of 3(5)-mercapto--1,2,4-triazole is melt and allowed to stand at 120 °C for an hour. The cooled reaction mixture is treated with 5 ml of hot ethanol, cooled and filtered. Thus 1.90 g of the desired compound are obtained, yield 65 %. Mp.: 201 - 202 °C.

Example 14

4-(1H-1,2,4-triazole-1-yl)-2,8-dimethyl--5-chloro-quinoline

A mixture of 2.26 g of 4,5-dichloro-2,8--dimethyl-quinoline, 1.38 g of 1,2,4-triazole and

0.1 g of 96 % sulfuric acid is stirred at 70 °C for 3 hours. The reaction mixture is poured into 50 ml of water and neutralized with 1 ml of a concentrated ammonium hydroxide solution. The precipitated product is filtered and washed with water. Thus 2.0 g of the desired compound are obtained, yield 77.4 %. Mp.: 117-118 °C.

Example 15

4-[5(3)-methyl-1H-1,2,4-triazole-3(5)-yl-mercapto]-2-methyl-7,8-dichloro-quinoline

A mixture of 2.46 g of 2-methyl-4,7,8-trichloro-quinoline, 1.38 g of 3(5)-mercapto-5(3)-methyl-1,2,4-triazole and 10 ml of dimethyl formamide is stirred at 100 °C for 8 hours. The reaction mixture is poured into 100 ml of water, neutralized and the precipitated product is filtered. Thus 3.10 g of the desired compound are obtained, yield 95 %. Mp.: 156 - 158 °C.

Example 16

2-(1H-1,2,4-triazole-1-yl)-3-methyl-7-ethyl-quinoline

A mixture of 2.05 g of 2-chloro-3-methyl-7-ethyl-quinoline, 1.05 g of 1,2,4-triazole-hydrochloride, 0.69 g of 1,2,4-triazole and 10 ml of dimethyl formamide is stirred at 100 °C for 6 hours. The reaction mixture is poured into 100 ml of water, neutralized and the crude product is recrystallized from a mixture of ethanol and hexane. Thus 1.52 g of the desired compound are obtained, yield 64 %. Mp.: 72 - 73 °C.

Example 17

2-[1H-1,2,4-triazole-3(5)-yl-mercapto]--4-methyl-quinoline

A mixture of 1.78 g of 2-chloro-4--methyl-quinoline, 1.21 g of 3(5)-mercapto-1,2,4--triazole and 10 ml of dimethyl formamide is stirred at 40 °C for 3 hours. The reaction mixture is poured into 100 ml of water, neutralized and filtered. Thus 2.37 g of the desired compound are obtained, yield 98 %, m.p.: 96 - 98 °C.

Example 18

3-[5(3)-ethyl-1H-1,2,4-triazole-3(5)--yl-mercapto]-3,8-dimethyl-quinoline

1.91 g of 2-chloro-3,8-dimethyl-quinoline and 1.55 g of 3(5)-mercapto-5(3)-ethyl-1,2,4--triazole are reacted in an analoguous manner to Example 16. The crude product is recrystallized from a mixture of chloroform and ethanol. Thus 1.93 g of the desired compound are obtained, yield 68 %. Mp.: 190 - 192 °C.

Further compounds are prepared in an analoguous manner to the process described in the preceeding Examples. The compounds are disclosed in the following Table V. The number appearing in the column "method" relates to the number of the Example used for the preparation of the compound in caption.

Table V

Compounds of the general Formula (Ia)

Compound No.	R_1	R_2	R_3	R_4	Method	Yield (%)	Mp. °C
1	H	7-Cl	H	H	1	7o	169-17o
2	H	8-CH_3	H	H	1	81	142-144
3	H	8-CF_3	H	H	4	75	146-147
4	2-CH_3	H	H	H	3	57	88-89
5	2-CH_3	6-CH_3	H	H	3	71	11o-112
6	2-CH_3	8-CH_3	H	H	1	88	98-1oo
7	2-CH_3	6-OCH_3	H	H	3	87	117-118
8	2-CH_3	8-OCH_3	H	H	3	68	179-18o
9	2-CH_3	6-Cl	H	H	3	58	173-175
1o	2-CH_3	8-Cl	H	H	4	97	142-144
11	2-CH_3	7-CF_3	H	H	4	93	68-7o
12	2-CH_3	8-CF_3	H	H	4	86	154-156

13	2-CH_3	6-OH	H	H	1	4o	238-24o
14	2-CH_3	6-$COCH_3$	H	H	1	28	189-19o
15	2-CH_3	7-$COOCH_3$	H	H	1	49	184-186
16	2-CH_3	8-CH	H	H	4	57	2o8-21o
17	2-CH_3	5-Cl	8-CH_3	H	1	88	113-115
18	2-CH_3	6-Cl	8-CH_3	H	4	5o	173-175
19	2-CH_3	7-Cl	8-CH_3	H	4	98	147-149
2o	2-CH_3	5-Cl	8-Cl	H	1	74	123-124
21	2-CH_3	6-Cl	8-Cl	H	4	93	22o-222
22	2-CH_3	7-Cl	8-Cl	H	4	93	168-17o
23	2-CH_3	5-Cl	8-OCH_3	H	1	59	188-19o
24	2-CH_3	5-CH_3	7-CH_3	H	1	59	119-121
25	2-CH_3	5-CH_3	8-CH_3	H	1	64	12o-122
26	2-CH_3	6-CH_3	8-CH_3	H	1	66	129-131

27	2-CH_3	7-CH_3	8-CH_3	H	1	62	128-130
28	2-CH_3	5-CH_3	8-$NHCOCH_3$	H	1	57	232-234
29	2-CH_3	5-CH_3	8-NH_2	H	1	35	205-207
30	2-CCl_3	6-CH_3	H	H	4	50	102-104
31	2-CCl_3	8-CH_3	H	H	4	61	130-132
32	2-CCl_3	8-OCH_3	H	H	4	31	169-170
33	2-CCl_3	8-Cl	H	H	5	40	133-135
34	2-CCl_3	6-CCl_3	H	H	5	47	162-163
35	2-CCl_3	8-CCl_3	H	H	5	50	157-158
36	2-CCl_3	8-CF_3	H	H	5	47	132-133
37	2-CCl_3	6-Cl	8-Cl	H	5	73	157-159
38	2-CF_3	8-CF_3	H	H	5	73	106-107
-	-	-	-	-	-	-	-

Compound of the general Formula (Ib)

Compound No.	R_1	R_2	R_3	R_4	Method	Yield (%)	Mp. °C
39	H	7-Cl	H	H	7	77	161-162
4o	2-CH_3	H	H	H	7	66	181-182
41	2-CH_3	6-CH_3	H	H	7	59	167-169
42	2-CH_3	8-CH_3	H	H	7	71	143-145
43	2-CH_3	6-OCH_3	H	H	7	98	191-192
44	2-CH_3	8-OCH_3	H	H	7	77	186-187
45	2-CH_3	6-Cl	H	H	7	68	194-195
46	2-CH_3	8-Cl	H	H	7	88	199-2oo
47	2-CH_3	7-CF_3	H	H	7	76	2o5-2o7
48	2-CH_3	8-CF_3	H	H	7	42	183-184
49	2-CH_3	5-Cl	8-CH_3	H	7	78	184-186
5o	2-CH_3	6-Cl	8-CH_3	H	7	66	197-199

51	2-CH_3	7-Cl	8-CH_3	H	7	79	168-170
52	2-CH_3	6-Cl	8-Cl	H	7	65	206-207
53	2-CH_3	7-Cl	8-Cl	H	7	87	199-200
54	2-CCl_3	6-CH_3	H	H	15	72	127-129
55	2-CCl_3	8-CH_3	H	H	6	40	166-168
56	2-CCl_3	8-Cl	H	H	6	55	188-189
57	2-CCl_3	8-CCl_3	H	H	6	18	129-130
58	2-CCl_3	8-CF_3	H	H	6	50	190-192
59	2-CCl_3	6-Cl	8-Cl	H	6	48	214-215
60	2-CF_3	8-CF_3	H	H	6	24	208-210
61	H	7-Cl	H	CH_3	7	65	227-228
62	2-CH_3	H	H	CH_3	15	82	175-177
63	2-CH_3	6-CH_3	H	CH_3	15	78	181-182
64	2-CH_3	8-CH_3	H	CH_3	15	85	198-200

65	2-CH_3	6-OCH_3	H	CH_3	15	98	192-193
66	2-CH_3	8-OCH_3	H	CH_3	15	98	186-187
67	2-CH_3	8-CF_3	H	CH_3	15	96	18o-182
68	2-CH_3	6-Cl	8-CH_3	CH_3	15	99	2o7-2o8
69	2-CH_3	7-Cl	8-CH_3	CH_3	15	62	191-193
7o	2-CH_3	6-Cl	8-Cl	CH_3	15	38	2o9-211
71	2-CH_3	7-Cl	8-Cl	CH_3	15	95	156-158
72	H	7-Cl	H	CH_2CH_3	7	79	154-156
73	2-CH_3	H	H	CH_2CH_3	7	44	135-137
74	2-CH_3	6-CH_3	H	CH_2CH_3	7	36	171-172
75	2-CH_3	8-CH_3	H	CH_2CH_3	7	85	176-177
76	2-CH_3	6-OCH_3	H	CH_2CH_3	15	77	168-17o
77	2-CH_3	8-OCH_3	H	CH_2CH_3	7	3o	171-173
78	2-CH_3	8-CF_3	H	CH_2CH_3	15	81	162-165

79	$2\text{-}CH_3$	6-Cl	$8\text{-}CH_3$	CH_2CH_3	15	44	191-193
80	$2\text{-}CH_3$	7-Cl	$8\text{-}CH_3$	CH_2CH_3	15	72	155-156
81	$2\text{-}CH_3$	6-Cl	8-Cl	CH_2CH_3	15	85	177-178
82	$2\text{-}CH_3$	7-Cl	8-Cl	CH_2CH_3	15	32	172-174
-	-	-	-	-	-	-	-

Compounds of the general Formula (Ic)

Compound No.	R_1	R_2	R_3	R_4	Method	Yield (%)	Mp. °C
83	3-CH_3	H	H	H	16	71	79-8o
84	3-CH_3	6-CH_3	H	H	16	68	88-9o
85	3-CH_3	7-CH_3	H	H	16	87	79-8o
86	3-CH_3	8-CH_3	H	H	1o	3o	99-1o1
87	3-CH_3	6-CH_2CH_3	H	H	16	58	81-83
88	3-CH_3	7-CH_2CH_3	H	H	16	64	72-73
89	3-CH_3	8-CH_2CH_3	H	H	16	41	79-8o
9o	3-CH_3	6-OCH_3	H	H	1o	75	87-89
91	3-CH_3	6-Cl	H	H	1o	99	148-15o
92	3-CH_3	7-Cl	H	H	1o	98	119-12o
93	3-CH_3	5-CH_3	7-CH_3	H	16	7o	137-139
94	3-CH_3	6-CH_3	7-CH_3	H	16	62	117-119

95	3-CH_3	5-CH_3	8-CH_3	H	16	51	138-14o
96	3-CH_3	6-CH_3	8-CH_3	H	16	84	126-128
97	3-CH_3	7-CH_3	8-CH_3	H	16	76	118-119
98	3-CH_3	6-Cl	8-CH_3	H	1o	9o	194-195
99	3-CH_3	7-Cl	8-CH_3	H	1o	96	147-148
1oo	4-CH_3	H	H	H	16	99	111-113
1o1	4-CH_3	6-CH_3	H	H	16	71	134-136
1o2	4-CH_3	7-CH_3	H	H	1o	66	134-135
1o3	4-CH_3	8-CH_3	H	H	1o	63	124-126
1o4	4-CH_3	6-OCH_3	H	H	1o	71	124-126
1o5	4-CH_3	7-Cl	H	H	1o	66	193-195
1o6	4-CCl_3	6-CCl_3	H	CH_3	11	62	169-17o
-	-	-	-	-	-	-	-

Compounds of the general Formula (Id)

Compound No.	R_1	R_2	R_3	R_4	Method	Yield (%)	Mp. °C
1o7	3-CH_3	H	H	H	17	62	144-145
1o8	3-CH_3	6-CH_3	H	H	17	84	165-166
1o9	3-CH_3	7-CH_3	H	H	17	99	17o-171
11o	3-CH_3	8-CH_3	H	H	18	6o	124-125
111	3-CH_3	6-OCH_3	H	H	18	51	158-16o
112	3-CH_3	6-Cl	H	H	17	8o	188-19o
113	3-CH_3	7-Cl	H	H	17	8o	213-215
114	3-CH_3	6-Cl	8-CH_3	H	18	6o	19 -192
115	3-CH_3	7-Cl	8-CH_3	H	18	68	2o5-2o6
116	4-CH_3	H	H	H	17	98	96-98
117	4-CH_3	6-CH_3	H	H	18	92	125-126
118	4-CH_3	7-CH_3	H	H	18	74	134-136

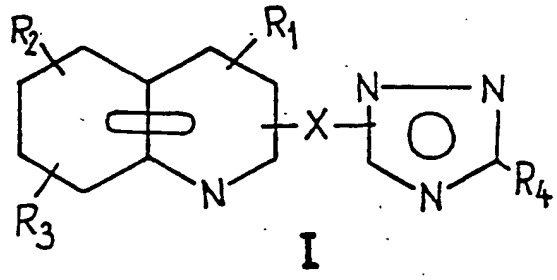
119	4-CH_3	8-CH_3	H	H	18	5o	135-137
12o	4-CH_3	6-OCH_3	H	H	18	81	152-154
121	4-CH_3	7-Cl	H	H	18	83	158-16o
122	3-CH_3	H	H	CH_3	17	84	211-212
123	3-CH_3	6-CH_3	H	CH_3	18	74	215-216
124	3-CH_3	7-CH_3	H	CH_3	17	85	2o4-2o5
125	3-CH_3	8-CH_3	H	CH_3	18	74	212-213
126	3-CH_3	6-OCH_3	H	CH_3	18	72	2o5-2o7
127	3-CH_3	6-Cl	H	CH_3	18	79	213-215
128	3-CH_3	7-Cl	H	CH_3	18	74	2o5-2o6
129	3-CH_3	6-Cl	8-CH_3	CH_3	18	4o	226-227
13o	3-CH_3	7-Cl	8-CH_3	CH_3	18	87	228-23o
131	4-CH_3	H	H	CH_3	17	78	172-174
132	4-CH_3	6-CH_3	H	CH_3	17	74	189-19o

133	4-CH_3	7-CH_3	H	CH_3	18	59	172-174
134	4-CH_3	8-CH_3	H	CH_3	18	67	188-19o
135	4-CH_3	6-OCH_3	H	CH_3	17	86	192-193
136	4-CH_3	7-Cl	H	CH_3	17	79	179-18o
137	3-CH_3	H	H	CH_2CH_3	17	85	187-189
138	3-CH_3	6-CH_3	H	CH_2CH_3	18	68	2o9-211
139	3-CH_3	7-CH_3	H	CH_2CH_3	17	57	145-146
14o	3-CH_3	8-CH_3	H	CH_2CH_3	18	68	19o-192
141	3-CH_3	6-OCH_3	H	CH_2CH_3	17	67	192-195
142	3-CH_3	6-Cl	H	CH_2CH_3	18	67	2o3-2o5
143	3-CH_3	7-Cl	H	CH_2CH_3	17	73	191-193
144	3-CH_3	6-Cl	8-CH_3	CH_2CH_3	18	5o	185-186
145	3-CH_3	7-Cl	8-CH_3	CH_2CH_3	18	72	214-215
146	4-CH_3	H	H	CH_2CH_3	17	92	13o-131

147	4-CH_3	6-CH_3	H	CH_2CH_3	18	37	132-133
148	4-CH_3	7-CH_3	H	CH_2CH_3	18	6o	117-118
149	4-CH_3	8-CH_3	H	CH_2CH_3	18	63	154-156
15o	4-CH_3	6-OCH_3	H	CH_2CH_3	18	4o	163-165
151	4-CH_3	7-Cl	H	CH_2CH_3	18	63	149-152
-	-	-	-	-	-	-	-

What we claim is:

1. Triazolyl quinoline derivatives of the general Formula (I)



(I)

I

(wherein

R^1 stands for hydrogen, methyl, trihalogenomethyl or carboxy;

R^2 is hydrogen, halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, phenoxy, amino, acetamino, C_{1-4} dialkylamino, acetyl, benzoyl, methylthio, carboxy, cyano, ethoxycarbonyl, nitro or trihalogenomethyl;

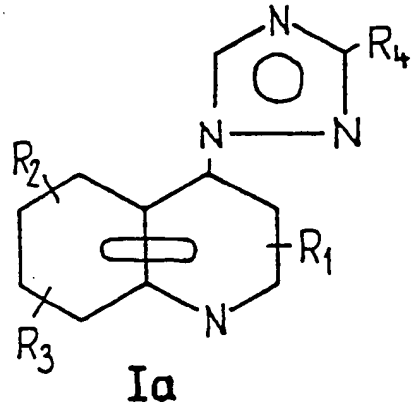
R^3 represents hydrogen, C_{1-4} alkyl or C_{1-4} alkoxy;

R^4 stands for hydrogen, methyl or ethyl and

X stands for a valency bond or -S-)

and acid addition salts thereof.

2. Compounds according to Claim 1 of the general Formula (Ia)

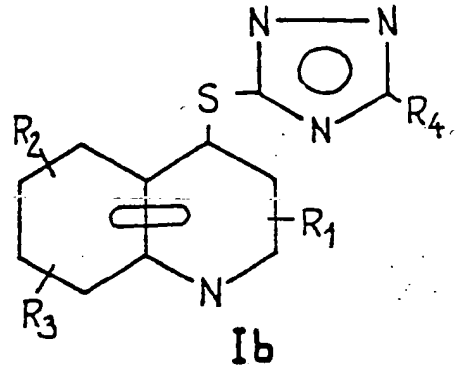


(Ia)

Ia

(wherein R^1, R^2, R^3 and R^4 are as stated in Claim 1) and acid addition salts thereof.

3. Compounds according to Claim 1 of the general Formula (Ib)

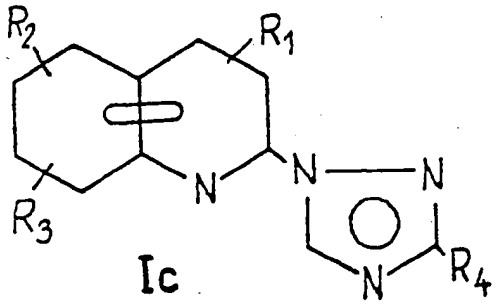


(Ib)

Ib

(wherein R^1, R^2, R^3 and R^4 are as stated in Claim 1) and acid addition salts thereof.

4. Compounds according to Claim 1 of the general Formula (Ic)

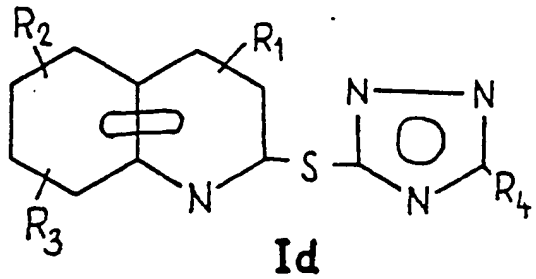


(Ic)

Ic

wherein R^1, R^2, R^3 and R^4 are as stated in Claim 1) and acid addition salts thereof.

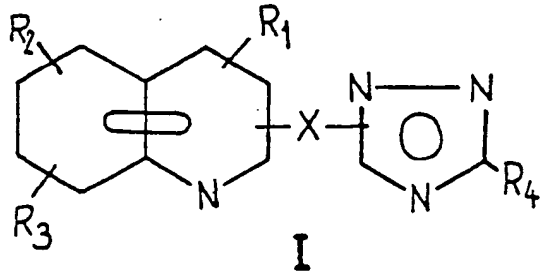
5. Compounds according to Claim 1 of the general Formula (Id)



Id (Id)

(wherein R^1, R^2, R^3 and R^4 are as stated in Claim 1) and acid addition salts thereof.

6. A process for the preparation of triazolyl quinoline derivatives of the general Formula (I)



I (I)

(wherein

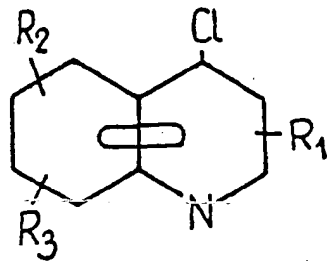
R^1 stands for hydrogen, methyl, trihalogenomethyl or carboxy;

R^2 stands for hydrogen, halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, phenoxy, amino, acetamino, C_{1-4} dialkylamino, acetyl, benzoyl, methylthio, carboxy, cyano, ethoxycarbonyl, nitro or trihalogenomethyl;

R^3 represents hydrogen, C_{1-4} alkyl or C_{1-4} alkoxy;

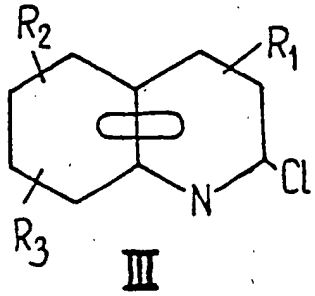
R^4 stands for hydrogen, methyl or ethyl and

X stands for a valency bond or -S-)
and acid addition salts thereof which comprises reacting a halogeno quinoline derivative of the general Formula (II)



(II)

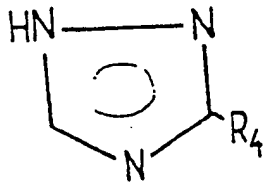
or (III)



(III)

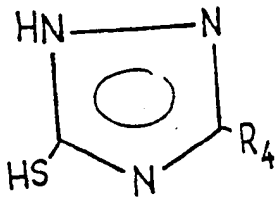
III

(wherein R^1, R^2 and R^3 are as stated above) with a 1,2,4-triazole of the general Formula (IV)



(IV)

or (V)



(V)

(wherein R^4 is as stated above) in the presence or absence of a solvent, in the presence or absence of an acid or a base, at a temperature between 0 °C and 200 °C and if desired, isolating the product thus obtained in the form of the free base or an acid addition salt thereof.

7. A process according to Claim 6 for the preparation of compounds of the general Formula (Ia) which comprises reacting a 4-chloro--quinoline derivative of the general Formula (II) with a 1,2,4-triazole of the general Formula (IV) (wherein R^1, R^2, R^3 and R^4 are as stated in Claim 6).

8. A process according to Claim 6 for the preparation of compounds of the general Formula (Ib) which comprises reacting a 4-chloro--quinoline derivative of the general Formula (II) with a 3-mercapto-1,2,4-triazole of the general Formula (V) (wherein R^1, R^2, R^3 and R^4 are as stated in Claim 6.).

9. A process according to Claim 6 for the preparation of compounds of the general Formula (Ic) which comprises reacting a 2-chloro--quinoline of the general Formula (III) with a 1,2,4-triazole of the general Formula (IV) (wherein R^1, R^2, R^3 and R^4 are as stated in Claim 6).

10. A process according to Claim 6 for the preparation of compounds of the general Formula (Id) which comprises reacting a 2-chloro--quinoline derivative of the general Formula (III) with a 3-mercapto-1,2,4-triazole of the general Formula (V) (wherein R^1, R^2, R^3 and R^4 are as stated in Claim 6.).

11. Pharmaceutical compositions comprising in an effective amount at least one compound of the

general Formula (I) (wherein R^1, R^2, R^3, R^4 and X are as stated in Claim 1) or a pharmaceutically acceptable acid addition salt thereof as active ingredient in admixture with suitable inert solid or liquid pharmaceutical carriers.

12. A process for the preparation of pharmaceutical compositions according to Claim 11 which comprises admixing at least one compound of the general Formula (I) or a pharmaceutically acceptable acid addition salt thereof with suitable inert solid or liquid pharmaceutical carriers.

13. Fungicidal compositions comprising as active ingredient in an effective amount at least one compound of the general Formula (I) (wherein R^1, R^2, R^3, R^4 and X are as stated in Claim 1) or an acid addition salt thereof in admixture with suitable inert solid or liquid carriers or diluents.

14. A process for the preparation of fungicidal compositions according to Claim 13 which comprises admixing at least one compound of the general Formula (I) or an acid addition salt thereof with suitable inert solid or liquid carriers or diluents.

15. A method for combating fungal diseases which comprises applying an effective amount of a fungicidal composition according to Claim 13 onto the plants, parts or environment thereof or the pests or the objects to be protected.

16. Compounds of the general Formula (I) and acid addition salts thereof whenever prepared by the process according to any of Claims 6-10.

17. A process as substantially disclosed herein with particular reference to the Examples.

INTERNATIONAL SEARCH REP RT

International Application No PCT/HU 86/00026

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 D 401/04, 401/12, //A 01 N 43/653, A 61 K 31/47, (C 07 D 401/04, 249:08, 215:12) (C 07 D 401/12, 249:08, 215:36)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
Int.Cl.[4]	C 07 D 401/04, 401/12

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

AT

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	Chemical Abstracts, vol. 99, no. 17, issued October 24, 1983 (Columbus, Ohio, USA), E. G. KNYSH "Synthesis and biological activity of some 5-heterylmercapto-1,2,4-triazoles", see page 592, column 1, abstract-no. 139 866z, Khim.-Form. Zh, 1983 17(7), 798-801 (Russ).	(1)
X	DE, A, 2 147 794 (MERCK) 30 March 1972 (30.03.72), see claim 1, page 4, lines 9-18.	(1,11)
A	Chemical Abstracts, vol. 94, no. 25, issued June 22, 1981 (Columbus, Ohio, USA), M. YOSHIDA "8-Quinolinesulfonyl tetrazolide as a coupling agent for oligonucleotides synthesis via triester approach", see page 631, column 2, abstract-no. 209 126f, Chiba Kogyo Daigaku Kenkyu Hokoku, Riko-hen 1980, 25, 53-9 (Japan).	(1)

[10] Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
23 June 1986 (23.06.86)	25 June 1986 (25.06.86)
International Searching Authority	**Signature of Authorized Officer**
AUSTRIAN PATENT OFFICE	

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SEC ND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	Chemical Abstracts, vol. 83, no. 23, issued December 8, 1975 (Columbus, Ohio, USA), J. J. BALDWIN "4-Trifluoromethylimidazoles and 5-(4-pyridyl)-1,2,4-triazoles, new classes of xanthine oxidase inhibitors", see page 14, column 1, abstract-no. 188 199n, J. Med. Chem. 1975, 18(9), 895-900 (Eng).	(1)
A	Chemical Abstracts, vol. 98, no. 17, issued April 25, 1983 (Columbus, Ohio, USA), P.K. KADABA "Triazolines", see page 572, column 2, abstract-no. 143 336y, J. Prakt. Chem. 1982, 324(5), 857-64 (Eng).	(1)

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

Annex to the International Search Report on International Patent Application No. PCT/HU 86/00026

Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned International search report. The Austrian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche internationale visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office autrichien des brevets.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
DE-A-2 147 794	30/03/1972	AU-A1- 33 427/71	22/03/197
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		CA-A1- 950 463	02/07/197
		CH-A - 562 813	13/06/197
		FR-A5- 2 107 984	12/05/197
		FR-B1- 2 107 984	01/08/197
		GB-A - 1 358 893	03/07/197
		JP-B4-49-046 622	11/12/197
		NL-A - 7 112 373	28/03/197
		US-A - 3 865 945	11/02/ 7
		US-A - 3 879 404	22/04/197
		US-A - 4 011 218	08/03/197
		US-A - 4 071 518	31/01/197
		US-A - 4 102 889	25/07/197
		US-A - 4 156 085	22/05/197
		US-A - 4 198 513	15/04/198
		US-A - 4 256 887	17/03/198